IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re:	Oleg Illich Epshtein *et al.*	Confirmation No:	7546
Application No:	10/552,650	Group:	1644
Filed:	January 22, 2005	Examiner:	Szperka, Michael Edward
For:	Medicinal Agent and Method for Curing Erectile Dysfunction		
Customer No.:	29127		
Attorney Docket No.	75.9US1		

DECLARATION UNDER 37 C.F.R. § 132 OF INVENTOR OLEG I. EPSHTEIN

1. I am Oleg I. Epshtein, a named inventor in the above-referenced U.S. patent application. I declare and affirm under the penalty of perjury under the laws of the United States that the following is true and correct based on my personal knowledge, or where not on my personal knowledge, on my information and belief.

2. I am the principal of the company "Materia Medica" which has been closely involved in the development and testing of the invention claimed in the referenced U.S. patent application.

3. I have read the Office Action dated July 9, 2007 in this application and have reviewed the grounds of rejection. In support of patentability of amended claims, I declare as follows.

4. The below-presented examples represent clinical trial data on efficacy and safety of the medicaments as claimed in the referenced application. The data were obtained in various medical universities and research institutes as specified in the attached data.

5. Example 1.

A study assessing efficacy and safety of ultra-low doses of endothelial NO synthase (e-NOS) antibodies in treatment of erectile dysfunction (ED) of varying etiology was conducted by clinical teams of Russian State Medical University (Moscow, Russia),

Volgograd State Medical University (Volgograd, Russia), I.M. Sechenov Moscow Medical Academy (Mocsow, Russia), S.P. Fedorov Saint-Petersburg urologist society (Saint-Petersburg, Russia). 169 males ages 18 to 70, diagnosed with ED of varying etiology took part in this multicenter double-blind placebo-controlled study. Patients were given ultra-low doses of e-NOS antibodies (12C+30C+200C) or placebo in form of orally dissolving tablets (1-2 tablets per diem), for a period of 12 weeks. The changes in International Index of Erectile Function (IIEF) scores were monitored, as well as the patient's assessment of treatment effectiveness.

The study has shown that application of ultra-low doses of to e-NOS antibodies correlated with statistically and clinically significant improvement of erectile function as well as improvement of other aspects of the patient's sexual quality of life. Particularly, IIEF score of erectile function increased from 17.4±0.4 to 24.0±0.3 in the group receiving treatment (17.9±0.7 in placebo group); erectile function restored to normal (EF>25) in 34% of treated patients (none in placebo group). Improvement of other aspects of sexual function (intercourse satisfaction, orgasmic function, libido, overall satisfaction) were also more pronounces in patients receiving the treatment compared to placebo. 3 cases (2%) of headaches and 1 case (0.7%) of nausea during the first week of treatment were registered in the treatment group; these did not require termination of treatment. 1 case (3.3%) of headaches was registered in the placebo group. Thus, adverse effects were not associated with the treatment.

We have thus demonstrated the efficacy and safety of ultra-low doses of antibodies to endothelial NO synthase for treatment of erectile dysfunction.

6. Example 2.

A study assessing efficacy and safety of ultra-low doses of endothelial NO synthase (e-NOS) antibodies in treatment of erectile dysfunction (ED) of varying etiology was conducted at Volgograd State Medical University and Research Institute of Urology. An open study included 120 males ages 18 to 70 diagnosed with erectile dysfunction (of varying etiology). The patients in the test category received ultra-low doses of e-NOS antibodies (12C+30C+200C) in form of orally dissolving tablets (1-2 tablets per diem); patients in the control category received 25-30 mg of sildenafil citrate (Viagra, Pfizer Inc, New York, NY) approximately 1 hour before anticipated sexual activity. The changes in International Index of Erectile Function (IIEF) scores were monitored, as well as the patient's assessment of treatment effectiveness.

The study has shown that administration of both ultra-low doses of e-NOS antibodies and sildenafil citrate consistently leads to the increase of integral factors characterizing the patient's sexual function. Based on the results from both categories, the capacity to increase erectile function was comparable for both treatments. In the experimental category, a positive response to the treatment (EF score increase of ≥ 3) was recorded in 56.7% of the cases; EF score was restored to normal levels (EF>25) in 30% of the cases. The results for the control sildenafil citrate category were 74.5% and 14%, respectively. The e-NOS antibodies treatment was well tolerated by the patients; a single reported case

of headaches was transient. Adverse side effects were observed in 20% of the patients of the control category; 6 of the patients had to discontinue the treatment after the first use due to increase in arterial blood pressure and headaches.

We have thus shown that the proposed treatment has the efficacy comparable to that of sildenafil citrate for treatment of erectile dysfunction while demonstrating a better safety profile.

7. Example 3.

This study of efficacy and safety of using ultra-low doses of antibodies to endothelial NO synthase (e-NOS) for treatment of erectile dysfunction (ED) in patients with ischemic heart disease (IHD) was conducted at Saratov Cardiology Research Institute (Saratov, Russia). The participants were diagnosed with IHD characterized by stable stress stenocardia of I and II functional classes and currently taking nitrates (immediate/sustained release). 30 males ages 40 to 65 diagnosed with erectile dysfunction (ED) of varying etiology participated in this open non-comparative study. The patients received ultra-low doses of antibodies to e-NOS (12C+30C+200C) in form of orally dissolving tablets (Impaza, 1-2 tablets per diem) in conjunction with the standard antianginal treatment (excluding beta-blockers and diuretics). Participants were monitored for changes of erectile function (EF) scores according to International Index of Erectile Function (IIEF), and patient's assessment of general effectiveness. Safety of the treatment was evaluated by assessment of adverse events and by monitoring the function of the cardiovascular system (arterial blood pressure, ECG, treadmill, Holter monitor, daily arterial blood pressure monitoring).

This study has shown an improvement of integral parameters of sexual function in patients receiving ultra-low doses of antibodies to e-NOS as follows: 62.3% improvement of erectile function score (from 16.1±0.67 to 26.13±0.43); erectile function restored to normal levels (EF>25) in 70% of patients. By week 12 of treatment, improvement of stable stress stenocardia of functional class I and II were also observed, evidenced by decrease of number of stenocardia incidents as well as the amount of nitrates taken per day and per week. The functional monitoring of the cardiovascular system performance has shown no change in the primary condition (IHD) and an increased tolerance to physical strain. During the study none of the patients complained of the worsening or alteration of the set of clinical IHD symptoms. The results of ECG and Holter monitoring did not change during the course of the treatment.

The efficacy and safety of using ultra-low doses of antibodies to e-NOS for treatment of ED of varying etiology is thus shown in IDH patients with stable stress stenocardia of functional class I and II, currently treated with nitrates.

8. Example 4.

The following study of effects of ultra-low doses of antibodies to endothelial NO synthase (e-NOS) on sexual motivation in male rats (Fischer 344, age 18 months) with

age-related suppression of the reproductive function was conducted at the Department of Medical Physiology and Department of Psychology, University of Tromsø (Tromsø, Norway). After the establishment of sexual behavior (during 4 weeks) four groups of rats (10 animals per group) received the following treatment intragastrically for four weeks: the proposed treatment (preparation of antibodies to e-NOS) once daily, 1ml or 3ml per animal; distilled water once daily, 1ml per animal (control); sildenafil citrate twice weekly, 3mg/kg in saline (comparison). Sexual motivation was assessed using Ågmo method (1997, 2003, 2004).

The study has demonstrated an increase of female preference score by 27.8% (as compared to the initial value) in the group receiving proposed treatment. The score was increased by 3.9% in the comparison group treated with sildenafil citrate and decreased by 3.9% in the control group.

This data demonstrates that the proposed treatment has a stimulating effect on sexual motivation of aged male rats with exhibited age-related suppression of copulatory function.

9. Example 5.

The following study of the effect of ultra-low doses of antibodies to endothelial NO synthase (e-NOS) on endothelial NO synthase activity, NO and cGMP production was conducted at the Research Institute of Pharmacology Tomsk Scientific Center (Tomsk, Russia). Groups of male rats (total number of animals n=90) were treated as follows: 1.5ml per animal of proposed treatment (preparation of antibodies to e-NOS) was administered intragastrically once or during 5 days; 1.5ml per animal of distilled water was administered intragastrically once or during 5 days (control); 10mg/kg of sildenafil citrate was administered intragastrically once or during 5 days (comparison). Animals were sacrificed following the treatment and homogenates cavernosal tissues were analyzed. NO synthase (NOS) activity and levels of NO derivatives (nitrites and nitrates) was assayed by colorimetric method; cGMP content was assayed by ELISA.

It was shown that a single oral administration of the proposed treatment led to a two-fold increase in NOS activity and to 1.4-fold increase in NO derivative content; the increase in cGMP content was not confirmed. Administration of sildenafil citrate led to a confirmed increase in cGMP content; however, there was no increase in NOS activity or in NO derivative content. After 5 day administration of the proposed treatment NOS activity in cavernosal tissues was increased 2.4-fold, NO derivative content was increased 1.4-fold and cGMP content – 4-fold compared to control.

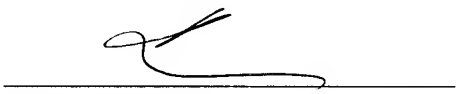
Thus, it was shown that single as well as sustained application of the proposed treatment stimulated NOS activity, NO and cGMP production. In contrast, application of sildenafil citrate influenced only cGMP content.

10. Example 6.

The following study of the effect of ultra-low doses of antibodies to endothelial NO synthase (e-NOS) on hemodynamic indicators of hypertensive rats was conducted at the Institute of Cytology and Genetocs (Novosibirsk, Russia). The study was conducted in 30 male rats of NISAG line. NISAG line is characterized by hereditary stress-induced arterial hypertension. Different groups of rats received following treatments intragastrically, for 10 days: proposed treatment (preparation of antibodies to e-NOS), 0.5ml per animal; distilled water, 0.5ml per animal (control); losartan, 10mg/kg in 2.5ml/kg of distilled water. Arterial blood pressure was measured before treatment, 2 hours after the first treatment, then on days 5 and 10 of treatment, and 7 days after the treatment was stopped.

The study has demonstrated that the proposed treatment decreases arterial blood pressure in hypertensive rats. This effect increased gradually – confirmed arterial blood pressure decrease of 10.7 mmHg was observed on day 10 of treatment. In comparison, the effect of losartan was observed on day 5 of treatment (arterial blood pressure decrease of 17.8 mmHg). No withdrawal syndrome was associated with either treatment.

10. The medicament as claimed in the referenced application is now available as an over the counter (OTC) medicament in Russian and several foreign countries. The sales of the claimed medicament have propelled it to one of the top 20 OTC medicaments with about 10 million items manufactured and sold.



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Date: December 26, 2007
Moscow, Russia